Comparative Analysis of In Vitro Release Kinetics Among Sultolin®, Ventolin®, Brodil® and Salbutal®

A thesis report submitted to the Department of Pharmacy, East West University, Bangladesh, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Kazi Ireen 24.12.09

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OBJECTIVE

The objective of the study is to do a comparative analysis of in vitro release kinetics among Sultolin® (Square Pharmaceuticals Ltd.), Ventolin® (Glaxo-Smith Klian Pharmaceuticals), Brodil® (ACI Pharmaceuticals Ltd.) and Salbutal® (Sunofi Aventis).

Declaration of Guide

This is to certify that Kazi Ireen, student of Department of Pharmacy, East West University, has performed this research titled "Comparative analysis of in vitro release kinetics among Sultolin® (Square Pharmaceuticals Ltd.), Ventolin® (GlaxoSmith Klian Pharmaceuticals Ltd.), Brodil® (ACI Pharmaceuticals Ltd.) and Salbutal® (Sunofi Aventis)"

Her work is genuine. I have gone through the research and the work is up to my satisfaction.

A·H·Pathan
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Abstract

Background: The purpose of this research work was to determine the in vitro release profile kinetics of four brands (Sultolin, Ventolin, Brodil and Salbutal) of salbutamol tablet of Bangladesh.

Method: Ten tablets from each brand were taken to perform thickness test, weight variation test, friability test and hardness test individually. Another two tablets from each brand were taken to do the dissolution test. Thickness tests were done using the Vernier Calipers. Weight variation tests were done using electronic weighing balance. Friability tests were done in the Roche Friabilator and hardness tests Monsanto Hardness Tester. The dissolution test was performed using dissolution tester (RC6, Vanguard Pharmaceuticals, USA). After dissolution test of the four brands absorbances were compared with the standard solution of crude salbutamol sulphate.

Result: The average thickness of Sultolin, Ventolin, Brodil and Salbutal were found 8.17mm, 8.42mm, 9.77mm and 6.32mm respectively. The % friability of Sultolin, Ventolin, Brodil and Salbutal were 0.37, 0.17, -0.14, -0.10 respectively. The mean hardness values of Sultolin, Ventolin, Brodil and Salbutal were 10.007N, 11.64N, 14.72 N and 13.04N respectively. Average weights of Sultolin, Ventolin, Brodil and Salbutal were found 0.17103gm, 0.20097gm, 0.19688gm and 0.10086gm respectively. No brand met the absorbance of standard salbutamol sulphate.

Conclusion: After conducting all the tests to determine various parameters, it has been found that, release profile kinetics of Sultolin, Ventolin, Brodil and Salbutal differed a lot from each other and also from the standard.

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Introduction

Salbutamol is a selective β-2 adrenoceptor agonist. At therapeutic doses it acts on the β-2 adrenoreceptors of pulmonary bronchial muscle with little or no action on the β-1 adrenoreceptors of cardiac muscle. (ADHB Govt, 2009)

Salbutamol is effective and used against common respiratory disease asthma.

Asthma is a chronic long-term lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. The coughing often occurs at night or early in the morning. The airways are tubes that carry air into and out of your lungs. People who have asthma have inflamed airways. This makes the airways swollen and very sensitive. They tend to react strongly to certain substances that are breathed in. When the airways react, the muscles around them tighten. This causes the airways to narrow, and less air flows to your lungs. The swelling also can worsen, making the airways even narrower. Cells in the airways may make more mucus than normal. Mucus is a sticky, thick liquid that can further narrow your airways. This chain reaction can result in asthma symptoms. Symptoms can happen each time the airways are irritated. Sometimes symptoms are mild and go away on their own or after minimal treatment with an asthma medicine. At other times, symptoms continue to get worse. When symptoms get more intense or additional symptoms appear, this is an asthma attack. Asthma attacks also are called flareups or exacerbations.

It's important to treat symptoms when someone first notices them. This will help prevent the symptoms from worsening and causing a severe asthma attack. Severe asthma attacks may require emergency care, and they can cause death. Asthma can't be cured. Even when one feels fine, he or she still has the disease and it can flare up at any time. But with today's knowledge and treatments, most people who have asthma are able to manage the disease. They can live normal, active lives and sleep through the night without interruption from asthma.

Asthma affects people of all ages, but it most often starts in childhood. In the United States, more than 22 million people are known to have asthma. Nearly 6 million of these people are children.

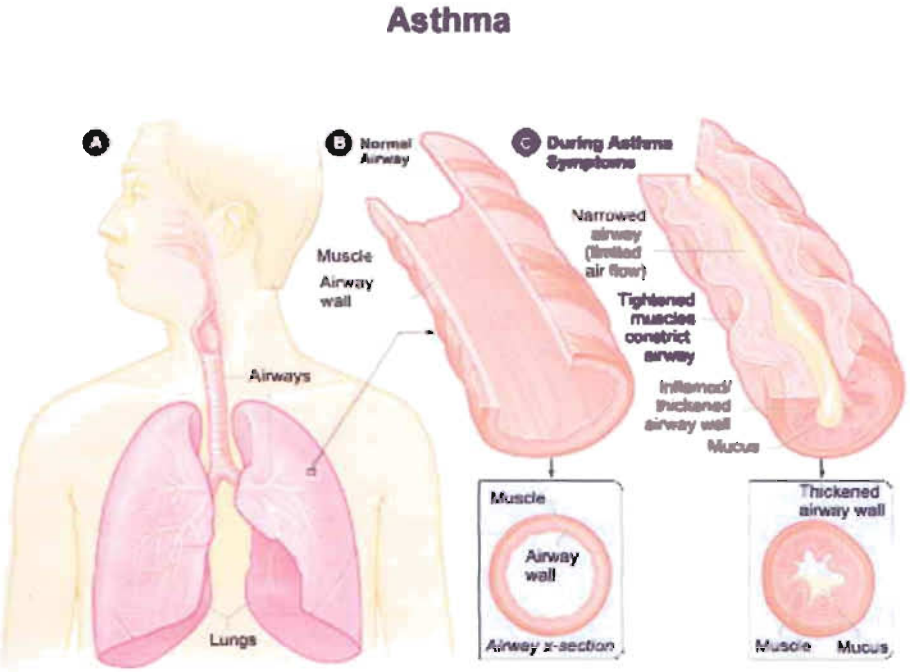


Figure 1: Asthma

Part A shows the location of the lungs and airways in the body. Part B shows a cross-section of a normal airway. Part C shows a cross-section of an airway during asthma symptoms.

Causes of Asthma

The exact cause of asthma isn't known. Researchers think a combination of factors such as family genes and certain environmental exposures interact to cause asthma to develop, most often early in life. These factors include:

- An inherited tendency to develop allergies, called atopy
- Parents who have asthma

- Certain respiratory infections during childhood
- Contact with some airborne allergens or exposure to some viral infections in infancy or in early childhood when the immune system is developing

If asthma or atopy runs in the family, exposure to airborne allergens (for example, house dust mites, cockroaches, and possibly cat or dog dander) and irritants (for example, tobacco smoke) may make ones airways more reactive to substances in the air he breathes.

Different factors may be more likely to cause asthma in some people than in others. Researchers continue to explore what causes asthma. (NHLBI, 2008)

Diagnosis of Asthma

While airway inflammation and airway hyperreactivity are characteristic of asthma, it is not necessary to demonstrate either in order to diagnose asthma. Demonstration of reversible airway obstruction is the clinical criterion for asthma. The clinical manifestations are generally some combination of cough, dyspnea, chest tightness, and wheez-ing. Tachypnea, tachycardia, use of accessory muscles, and pulsus paradoxus are physical findings that may also occur. There is a variety of methods acceptable for demonstration of reversible airway obstruction. The classic method is to demonstrate reversibility of obstructed pulmonary functions with a bronchodilator. Sometimes, other medications, such as corticosteroids, are required for normalizing pulmonary functions. Pulmonary functions are not always required to diagnose asthma. Historic information, such as cough and dyspnea occurring after exercise and relieved by bronchodilator, will often suffice. Clinical evaluation, such as wheezing and tachypnea that occur with a respiratory infection and reverse with administration of a n-agonist, will also suffice. While recurrent episodes of cough, dyspnea, and wheezing are almost always due to asthma, clinicians must be aware that there are other causes of airway obstruction manifested in a fashion similar to asthma.

Classification of Asthma by Etiology

A. Extrinsic asthma

B. Intrinsic asthma

C. Mixed asthma

D. Potentially fatal asthma

E. Aspirin-induced asthma

F. Occupational asthma

C. Exercise-induced asthma

H. Cough-equivalent asthma

I. Factitious asthma

J. Coexistent asthma and COPD (Grammer, L.C., et al, 2009)

Classification of Asthma by Severity

A. Mild Intermittent asthma (comes and goes)
When asthma is not well controlled, patient has asthma symptoms twice a week or less, and he is bothered by symptoms at night twice a month or less.

B. Mild persistent asthma
When asthma is not well controlled, patient has asthma symptoms more than twice a week, but no more than once in a single day. He is bothered by symptoms at night more than twice a month.. He may have asthma attacks that affect your activity.

C. Moderate persistent asthma
When asthma is not well controlled, the patient has asthma symptoms every day, and he

is bothered by nighttime symptoms more than once a week. Asthma attacks may affect his activity.

D. Severe persistent asthma
When asthma is not well controlled, the patient has symptoms throughout the day on most days, and he is bothered by nighttime symptoms often. In severe asthma, his physical activity is likely to be limited.

Anyone with asthma can have a severe attack - even those who have intermittent or mild persistent asthma. (UH Online, 2009)

Prevalence of Asthma and Allergies World-wide

Asthma has increased in nearly every part of the world studied, even in populations where the gene pool has not altered much in recent years.

The interplay between the genes and environment is an intriguing one. Migration studies have shown that asthma prevalence and bronchial hyper reactivity increase as a Western lifestyle is adopted.

This has not only been shown in Africa, but also in other parts of the world, e.g. China Hong Kong, South America and the Middle East.

In developed countries such as the USA it has been observed that certain ethnic groups who now reside there have higher prevalences and more severe asthma than other ethnic groups. This is illustrated by higher prevalences and more severe asthma in American Puerto Ricans than in those of Mexican origin. Such differences have suggested that there may be susceptibility genes which facilitate the development of asthma in a certain environment. Conversely, other genes may protect against the development of asthma.

Genes which may have been believed to influence the development of asthma include the beta-2 receptor gene, genes for the expression of the glucocorticoid-binding receptor and those responsible for the expression of allergy.

Recently Professor Eugene Bleeker discussed the current status of candidate genes for asthma in the World Allergy Organisation's 'Conversations in Allergy' on line, at the American Academy of Asthma, Allergy and Immunology (AAAAI) Congress in Philadelphia, March 2008.

Beta-2 receptor gene polymorphisms are believed to influence not only asthma severity, but also response to beta-2 short-acting and long-acting agonists. There are now 27 variations of the human beta-2 receptor gene.

Regarding the Arg/Gly polymorphism, 12-14% of American Caucasians are homozygous and 22-24% of African Americans are homozygous.

Individuals who have the Arg/Arg haplotype behave differently compared with those who have the Arg/Gly haplotype, when they receive intermittent versus regular short-acting beta-2 agonists. It has been of interest to note that the Puerto Ricans in the USA generally have been receiving frequent treatment with short-acting beta-2 agonists. For the long-acting beta-2 agonists however, detrimental effects have not been shown to be related to the presence of an Arg/Arg polymorphism of the beta-2 adrenergic receptor in studies of both formoterol and Serevent, used in combination with a steroid.

Other asthma susceptibility genes:

There are a number of genes being studied because they influence the expression of proteins, molecules and cytokines, which are important in the immunopathology of asthma and allergies.

Important susceptibility genes include the IL4 receptor alpha gene, IL4 gene, the IL13 gene, Stat 6 genes regulating IgE expression, Adam 33 and the HLA-G genes.

Variations in the IL4 receptor gene have correlated functionally with a population of severe asthmatics who have required ICU admission, mechanical ventilation and persistent eosinophilia.

Current studies in progress by Professor Donetta Vercelli (Arizona), also highlighted at the AAAAI meeting in March 2008, indicate that variations in the promoter for the IL13 gene influence transcription in B cells and may influence transcription of IgE by up to 50%.

Although TNF[alpha] is believed to play an important role in severe asthma, therapeutic studies with anti-TNF[alpha] have been disappointing. In spite of this, rare genotypes for TNF[alpha] have been associated with more severe exacerbations and may represent a genetic marker for severity.

Studies looking at the efforts of combinations of different genes in asthma are on the horizon. Clustering of certain genotype polymorphisms may well identify the asthmatic who is likely to be more severe and require intensive treatment and surveillance. In addition gene mapping may also guide the clinician as to which anti-asthma medications may be more effective, or should be avoided in view of possible side-effects.

With the availability of gene microchips and microarray technology it may be cost effective and worthwhile to identify and profile a host of asthma genes in a particular severe asthmatic using computerized technology, to guide the clinician to the most appropriate treatment for a given patient, bearing in mind the wide heterogeneity of the asthmatic phenotypes in the population.

Reasons for the increase in asthma and allergy prevalence:

In addition to genetic factors, environmental factors play a critical role in the expression of allergic diseases. Examples of external factors which influence the expression of asthma and allergies are lack of exercise, obesity, changes in diet, Western lifestyle, time of exposure to allergen, context of exposure to allergens, breast-feeding, the indoor environment and reduction in childhood infections as a result of immunization.

Many of these environmental-host effects are explained by the important immunological processes which take place in the first 2 years of life, which normally protect one from developing allergies. (Potter, P.C., et al, 2009)

Asthma in Bangladesh

Asthma is an important chronic disorder of the airways with significant morbidity and mortality. Around 300 million people in the world currently have asthma. It is estimated that there may be an additional 100 million people with asthma by 2025.

According to First National .Asthma Prevalence Study (NAPS) 1999, in Bangladesh about 7 million people (5.2% of the population) are suffering from current asthma (at least three episodes of asthma attack in last 12 months). More than 90% of them do not take modern treatment. Unfortunately, majority of these patients are in 1-15 years of age group, that is, 7.4% of the total pediatric population of our country is suffering from asthma. The following points have been noted from the said study:

• Asthma is more prevalent in children than in adults

• Asthma and all other allergic conditions are more prevalent in male children than in females

• Other atopic diseases (allergic rhinitis, allergic conjunctivitis and atopic

dermatitis) are more common in older children than younger ones

• Asthma is more frequent in coastal and rural areas than in urban areas

The disease causes physical, emotional and financial sufferings for patients leading to a deleterious effect on the overall socio-economic structure of the country. Asthma accounts for about 1 in every 250 deaths worldwide, although modern management, which obviously includes patient education, can prevent 80% of such death. The economic cost of asthma is considerable both in terms of direct · medical costs (such as hospital admissions . and cost of pharmaceuticals) and indirect medical costs (such as loss of work-time and premature death). Due to advances in the field of medicine, great progress has been achieved in the treatment of asthma. Latest scientific concepts about asthma pathogenesis and management have revolutionized its treatment.

With the combination of preventer, reliever and protector drugs and patient education we can offer an almost normal life to an asthma patient.

There are many false beliefs among the people of our country regarding asthma and its various management aspects. Being part and parcel of the community, many physicians also have such misconceptions. A study conducted among the health care providers of Bangladesh, from qualified consultants down to quacks, regarding perception and practice of asthma management revealed a disappointing picture. The study found that Chest x-ray was the only investigation advised to support the diagnosis of asthma. Spirometry and pulse oximetry were almost non-existent. For acute asthma management, use of nebulizer was limited to the consultants and physicians working at medical colleges. Use of rescue course of oral corticosteroids was bare minimum. Antibiotics use was found in large number of cases. There was rampant use of oral salbutamol, injectable aminophylline and ketotifen in the management of asthma. (Ahmed, M.M., et al, 2005)

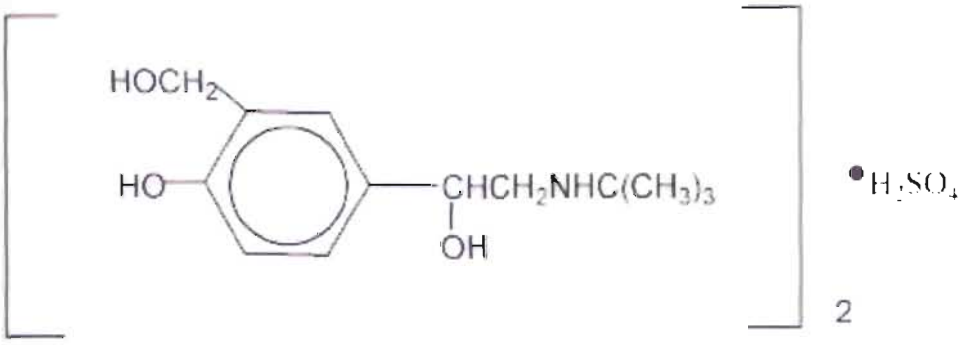
SALBUTAMOL

Salbutamol is a selective β-2 adrenoceptor agonist. It is used as a bronchodilator in the treatment of reversible bronchospasm. Its usual dose is 2-4 mg, 3-4 times a day1. It is generally administered as tablet, capsule, syrup and spray. Salbutamol is well absorbed following oral administration with peak plasma levels occuring within 1 to 4 hours (t_{max}). Despite the fact that salbutamol is well absorbed, its systemic bioavailability is only 50% due to extensive presystemic metabolism in the intestinal wall. Salbutamol is almost exclusively metabolised by conjugation to a 4'-o-sulphate ester in the intestinal wall and liver.

Chemistry and Physical Properties of Salbutamol

Salbutamol sulfate extended-release tablets contain salbutamol sulfate, the racemic form of salbutamol and a relatively selective beta2-adrenergic bronchodilator, in an extended-release formulation. salbutamol sulfate has the chemical name (±) a1-[(tert-butyl-

amino)methyl]-4-hydroxy-m-xylene-a, a′-diol sulfate (2:1) (salt), and the following structural formula:



salbutamol sulfate has a molecular weight of 576.7, and the molecular formula is (C13H21NO3)2•H2SO4. Salbutamol sulfate, USP is a white crystalline powder, soluble in water and slightly soluble in ethanol.

Each tablet for oral administration contains 4 mg or 8 mg of salbutamol as 4.8 mg or 9.6 mg, respectively, of salbutamol sulfate, USP. In addition each tablet contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, sodium lauryl sulfate, titanium dioxide, triacetin and xanthan gum. The 8 mg tablets also contain the following coloring agents: FD&C Blue #2 aluminum lake and FD&C Yellow #6 aluminum lake. (Daily Med, 2007)

One of the most interesting factors in the chemistry and biochemistry of salbutamol is the opposite biological effect observed for the R and S isomer of the drug. The R isomer effects dilation of the smooth muscle whereas the S isomer, via a different pathway, causes constriction of this same muscle. (Chem Wiki, 2009)

Indications and dosages

To prevent and relieve bronchospasm in patients with reversible obstructive airway disease:

Adults and children ages 12 and older: *Tablets* - 2 to 4 mg P.O. three or four times daily, not to exceed 32 mg daily. *Extended-release tablets* - 4 to 8 mg P.O. q 12 hours, not to exceed 32 mg daily in divided doses. *Syrup* - 2 to 4 mg (1 to 2 tsp or 5 to 10 ml) three or four times daily, not to exceed 8 mg q.i.d. *Aerosol* - one to two inhalations q 4 to 6 hours to relieve bronchospasm; two inhalations q.i.d. to prevent bronchospasm. *Solution for inhalation* - 2.5 mg three to four times daily by nebulization, delivered over 5 to 15 minutes.

Children ages 6 to 12: *Tablets* - 2 mg P.O. three or four times daily; maximum daily dosage is 24 mg, given in divided doses. *Extended-release tablets* - 4 mg q 12 hours; maximum daily dosage is 24 mg/kg given in divided doses. *Syrup* - 2 mg (1 tsp or 5 ml) three or four times daily, not to exceed 24 mg.

Children ages 2 to 12 weighing more than 15 kg (33 lb): *Solution for inhalation* - 2.5 mg three to four times/day by nebulization

Children ages 2 to 6: *Syrup* - Initially, 0.1 mg/kg P.O. t.i.d., not to exceed 2 mg (1 tsp) t.i.d. Maximum dosage is 4 mg (2 tsp) t.i.d.

To prevent exercise-induced bronchospasm:

Adults and children older than age 4 (older than age 12 with Proventil): Two inhalations 15 minutes before exercise.

Clinical Pharmacology of Salbutamol

Salbutamol stimulates the production of intracellular cyclic AMP, enhancing the binding of intracellular calcium to the cell membrane and endoplasmic reticulum, resulting in bronchodilation. Also enhances mucociliary clearance. Activation of the β-2 adreno-receptors opens ATPase channels and drives potassium from the extracellular to the intracellular space. This both decreases extracellular hyperkalaemia and increases intracellular potassium, so decreasing the chance of arrhythmias. Face mask is not significantly systemically absorbed via the lungs. A proportion of the dose may be swallowed and can be readily absorbed from the gastrointestinal tract. First pass metabolism of salbutamol occurs in the liver. About half is excreted in the urine as an inactive sulphate conjugate, and about 30% is excreted as unchanged salbutamol. (ADHB, 2009)

In vitro studies and in vivo pharmacologic studies have demonstrated that salbutamol has a preferential effect on beta-adrenergic receptors. While it is recognized that beta-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicates that there is a population of beta-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these receptors has not been established. The pharmacologic effects of beta-adrenergic agonist drug salbutamol, is at least in part attributable to stimulation through beta-adrenergic receptors on intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells. Salbutamol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, while producing fewer cardiovascular effects. (WIWISS, 2009)

Pharmacokinetics of Salbutamol

Salbutamol is readily absorbed from the gastrointestinal tract, maximum plasma concentrations occurring within 2.5 hours. It is subject to first pass metabolism in the liver. The plasma half-life ranges from 2.7-7.0 hours. Elimination occurs by both metabolism and urinary excretion. 76% of an oral dose is excreted over 3 days with the majority of the dose excreted within the first 24 hours.

Salbutamol is metabolised to a sulphate conjugate accounting for 50% of an oral dose. About half is excreted in the urine as an inactive sulphate conjugate, following oral administration (the rest being unchanged salbutamol), whereas rather less is excreted as the conjugate following intravenous administration. Unlike isoprenaline, salbutamol is not inactivated by catechol-o-methyl-transferase (COMT) or sulphatase enzymes.

After inhalation therapy, systemic absorption is low, maximum serum concentrations occurring within 2-4 hours. Salbutamol does not appear to be metabolised in the lung, therefore its behaviour following inhalation depends upon the delivery method used, which determines the proportion of inhaled salbutamol relative to proportion inadvertently swallowed.

Urinary studies indicate an elimination half-life of approximately four hours. Of that which is absorbed, 72% is excreted with 24 hours in the urine, 28% as unchanged salbutamol and 44% as the sulphate conjugate. Salbutamol does not pass the blood-brain barrier. (Medsafe, 1999)

Containdications

Salbutamol sulfate extended-release tablets are contraindicated in patients with a history of hypersensitivity to salbutamol or any of its components.

Warnings

Immediate hypersensitivity reactions may occur after administration of salbutamol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

Cardiovascular Effects

Salbutamol sulfate extended-release tablets, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salbutamol sulfate extended-release tablets at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, salbutamol sulfate extended-release tablets, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of salbutamol sulfate extended-release tablets than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment; e.g., corticosteroids.

Paradoxical Bronchospasm

Salbutamol sulfate extended-release tablets can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, salbutamol sulfate

extended-release tablets should be discontinued immediately and alternative therapy instituted.

Rarely, erythema multiforme and Stevens-Johnson Syndrome have been associated with the administration of oral salbutamol in children.

Drug Interactions

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Salbutamol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salbutamol on the vascular system may be potentiated.

Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as salbutamol sulfate extended-release tablets, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with nonpotassium-sparing diuretics.

Digoxin

Digoxin level decreases with single-dose intravenous and oral administration of salbutamol. It would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and salbutamol.

Pregnancy

Salbutamol gives teratogenic effects in pregnancy category C.

Overdose

Overdose of salbutamol sulphate include seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Hypokalemia may also occur. As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of salbutamol sulfate extended-release tablets. (Daily Med, 2007)

Absorption:

In pharmacokinetics, absorption is defined as the amount of drug that reaches the general circulation unchanged. Hence, that which is metabolized or chemically transformed at the site of application or in transit is by definition not absorbed. This definition arises mainly out of the necessity because of experimental and physiologic limitations in quantitating the manifestations of absorption in the intact animal or human. Absorption often refers to the overall transport of a drug and related substances into the body or parts thereof, e.g., the eyes or the skin. (Lachman, L., 1986)

Bioavailability:

The relative amount of an administered dose of a particular drug that reaches the systemic circulation intact and the rate at which this occurs is known as the bioavailability. Bioavailability is therefore defined as the rate and extent of drug absorption. The bioavailability exhibited by a drug is thus very important in determining whether a therapeutically effective concentration will be achieved at this site(s) of action.
In defining bioavailability in these terms, it is assumed that the administered drug is therapeutically active form. The definition would not be valid in the case of prodrugs, whose therapeutic action depends on their being converted into a therapeutically active form prior to or on reaching the systemic circulation. In the context of bioavailability, the term 'systemic circulation' refers primarily to venous blood (excluding the hepatic portal vein) and the arterial blood, which carries the intact blood to the tissues.
Therefore, for a drug which is administered orally to be 100% bioavailable, the entire dose must move from the dosage form to the systemic circulation. The drug must therefore:

- be completely released from the dosage form
- be fully dissolved in the gastrointestinal fluids
- be stable in solution in the gastrointestinal fluids
- pass through the gastrointestinal barrier into the mesenteric circulation without being metabolized
- pass through the liver into the systemic circulation unchanged.

Anything that adversely affects either the release of the drug from the dosage form, its dissolution into the gastrointestinal fluids, its permeation through and stability in the gastrointestinal barrier or its stability in the hepatic portal circulation will influence the bioavailability exhibited by that drug from the dosage form in which it was administered. (Aulton, M.E., 2007)

Thickness Study

At a constant compressive load, tablet thickness varies with changes in die fill, with particle size distribution and packing of the particle mix being compressed, and with tablet weight, while with a constant die fill, thickness varies with variations in compressive load. Tablet thickness is consistent batch to batch or within a batch only if the tablet granulation or powder blend is adequately consistent in particle size and size distribution, if the punch tooling is of consistent length, and if the tablet press is clean and in good working order. The crown thickness of individual tablets may be measured with a micrometer, which permits accurate measurements and provides information on the variation between tablets. Other techniques employed in production control involving placing 5 or 10 tablets in a holding tray, where there total crown thickness may be measured with a sliding caliper scale. This method is much more rapid than measurement with micrometer in providing an overall estimate of tablet thickness in production operations, but it does not a readily provide information on variability between tablets; however if the punch and die tooling has been satisfactorily standardized and the tablet machine is functioning properly, this method is satisfactory for production work. (Lachman, L., 1986)

Methodology: The objective of this study was to measure thickness of salbutamol tablets of four brands (Sultolin, Ventolin, Brodil and Salbutal) using Vernier Calipers. At first, a tablet was placed between two jaws horizontally. Then, the screw of the caliper was moved toward to hold the tablet and reading was taken in cm from the scale. Thickness was measured in mm. Then, the thicknesses of rest of the tablets were measured in the same procedure and the results were recorded in the Table1, Table2, Table3 and Table4.

Table1: Thickness of Sultolin

Sultolin					
Tab no.	**Reading of cm scale**	**Reading of vernier scale (mm)**	**Vernier constant (mm)**	**Vernier error (mm)**	**Thickness of tablet (mm)**
1	0.8	3	0.05	0.02	8.17
2	0.8	3	0.05	0.02	8.17
3	0.8	3	0.05	0.02	8.17
4	0.8	3	0.05	0.02	8.17
5	0.8	3	0.05	0.02	8.17
6	0.8	3	0.05	0.02	8.17
7	0.8	3	0.05	0.02	8.17
8	0.8	3	0.05	0.02	8.17
9	0.8	3	0.05	0.02	8.17
10	0.8	3	0.05	0.02	8.17

Table2: Thickness of Ventolin

Ventolin					
Tab no.	**Reading of cm scale**	**Reading of vernier scale (mm)**	**Vernier constant (mm)**	**Vernier error (mm)**	**Thickness of tablet (mm)**
1	0.8	8	0.05	0.02	8.42
2	0.8	8	0.05	0.02	8.42
3	0.8	8	0.05	0.02	8.42
4	0.8	8	0.05	0.02	8.42
5	0.8	8	0.05	0.02	8.42
6	0.8	8	0.05	0.02	8.42
7	0.8	8	0.05	0.02	8.42
8	0.8	8	0.05	0.02	8.42
9	0.8	8	0.05	0.02	8.42
10	0.8	8	0.05	0.02	8.42

Table3: Thickness of Brodil

Brodil					
Tab no.	**Reading of cm scale**	**Reading of vernier scale (mm)**	**Vernier constant (mm)**	**Vernier error (mm)**	**Thickness of tablet (mm)**
1	0.9	15	0.05	0.02	9.77
2	0.9	15	0.05	0.02	9.77
3	0.9	15	0.05	0.02	9.77
4	0.9	15	0.05	0.02	9.77
5	0.9	15	0.05	0.02	9.77
6	0.9	15	0.05	0.02	9.77
7	0.9	15	0.05	0.02	9.77
8	0.9	15	0.05	0.02	9.77
9	0.9	15	0.05	0.02	9.77
10	0.9	15	0.05	0.02	9.77

Table4: Thicknes of Salbutal

Salbutal					
Tab no.	**Reading of cm scale**	**Reading of vernier scale (mm)**	**Vernier constant (mm)**	**Vernier error (mm)**	**Thickness of tablet (mm)**
1	0.6	6	0.05	0.02	6.32
2	0.6	6	0.05	0.02	6.32
3	0.6	6	0.05	0.02	6.32
4	0.6	6	0.05	0.02	6.32
5	0.6	6	0.05	0.02	6.32
6	0.6	6	0.05	0.02	6.32
7	0.6	6	0.05	0.02	6.32
8	0.6	6	0.05	0.02	6.32
9	0.6	6	0.05	0.02	6.32
10	0.6	6	0.05	0.02	6.32

Discussion: After measuring all the tablets it was seen that, there was no variation in the thickness in tablets of same brand, but the thickness varied for

different brands. The thickness of Sultolin, Ventolin, Brodil and Salbutal were found 8.17mm, 8.42mm, 9.77mm and 6.32mm respectively. So it can be said that, Brodil has the highest thickness value and Salbutal has the lowest thickness value.

Result: From the above discussion we can say that, Salbutal is supposed to be released more faster than the other three brands.

Weight Variation Study:

The weight of the tablet being made is routinely measured to help ensure that a tablet contains the proper amount of drug. In practice composite samples of tablets (usually 10) are taken and weighed throughout the compression process. The composite weight divide by 10, however, provides an average weight but contains the usual problems averaged values. Within the composite sample that has an acceptable average weight, there could be tablet excessively overweight or underweight. To help alleviate this problem the United States Pharmacopoeia (USP)/National Formulary (NF) provides limits for the permissible variations in the weights of individual tablets expressed as a percentage of the average weight individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. (Lachman, L., 1986)

Methodology: The objective of this test was to determine the uniformity of weights of salbutamol tablets of four brands (Sultolin, Ventolin, Brodil and Salbutal) of Bangladesh using an electronic weighing balance. Initially, the individual weights of ten tablets of one brand were taken. Then the average weight of these tablets was determined. Similarly, the process was repeated for the rest three brands to determine individual and average weights of the tablets. Finally, the variations in weight were measured in gm using the following formula:**[(Average weight – Individual weight)/Average weight] × 100**

The data were recorded in Table5, Table6, Table7 and Table8.

Table5: Weight Variation of Sultolin

Tab no.	Wt. of Sultolin (gm)	Average wt. (gm)	Weight variation [(Average weight – Individual weight)/Average weight] × 100
1	0.172	0.17103	-0.57
2	0.1709		0.08
3	0.1697		0.78
4	0.1679		1.83
5	0.1725		-0.86
6	0.1698		0.72
7	0.1691		1.13
8	0.1727		-0.98
9	0.1718		-0.45
10	0.1739		-1.68

Line Chart1: Weight Variation of Sultolin

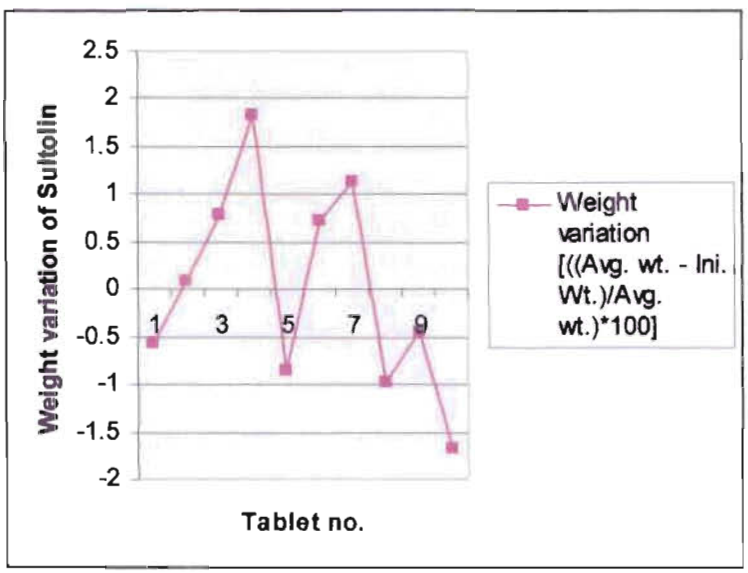


Table6: Weigh Variation of Ventolin

Tab no.	Wt of Ventolin(gm)	Avg wt (gm)	Weight variation [(Average weight – Individual weight)/Average weight] × 100
1	0.2054	0.20097	-2.20
2	0.2005		0.23
3	0.2011		-0.06
4	0.2015		-0.26
5	0.1987		1.13
6	0.2044		-1.71
7	0.1944		3.27
8	0.1994		0.78
9	0.2014		-0.21
10	0.2029		-0.96

Line Chart2: Weight Variation of Ventolin

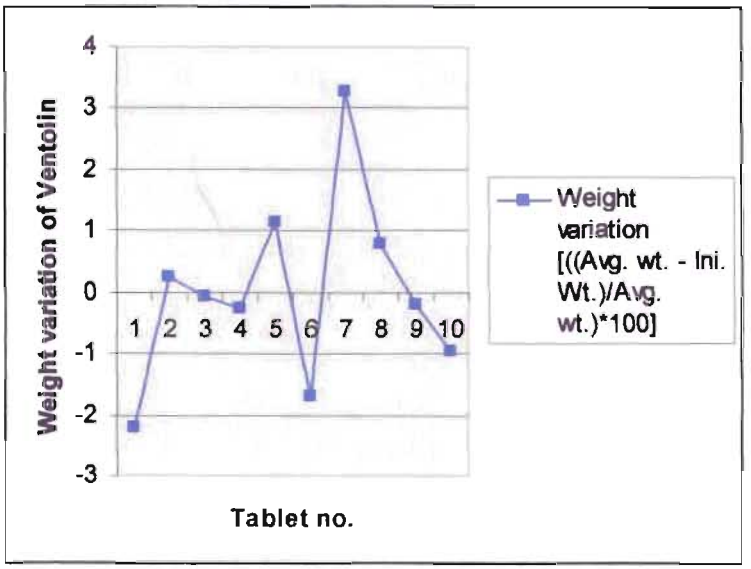


Table7: Weight Variation of Brodil

Tab no.	Wt of Brodil(gm)	Avg wt (gm)	Weight variation [(Average weight – Individual weight)/Average weight] × 100
1	0.1977	0.19688	-0.42
2	0.2016		-2.40
3	0.1901		3.44
4	0.1959		0.50
5	0.1984		-0.77
6	0.2009		-2.04
7	0.1952		0.85
8	0.1956		0.65
9	0.1979		-0.52
10	0.1955		0.70

Line Chart3: Weight Variation of Brodil

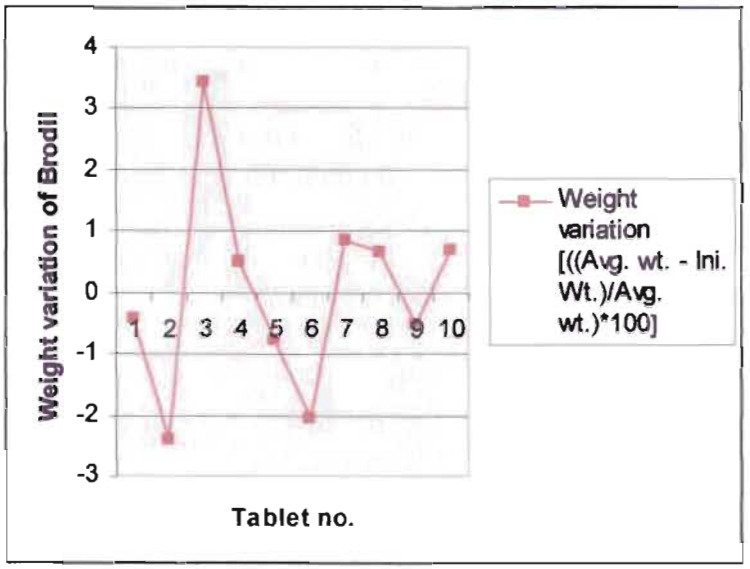
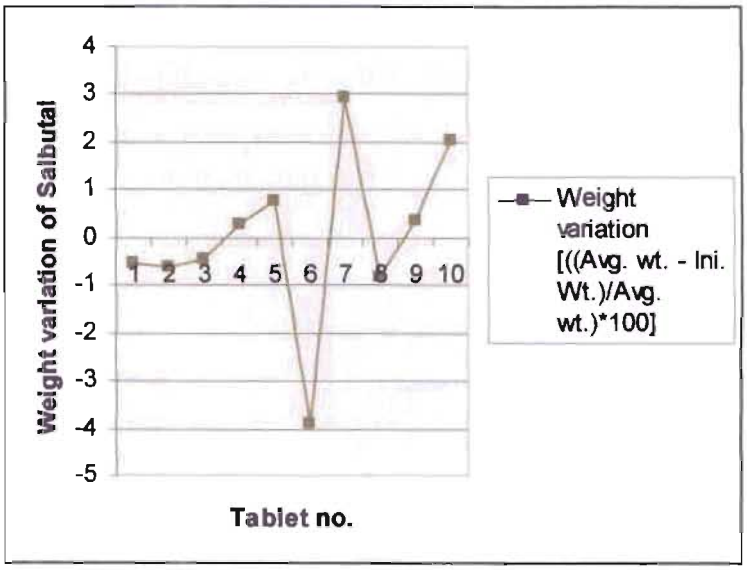


Table4: Weight Variation of Salbutal

Tab no.	Wt of Salbutal (gm)	Avg wt (gm)	Weight variation [(Average weight – Individual weight)/Average weight] × 100
1	0.1014	0.10086	-0.54
2	0.1015		-0.63
3	0.1013		-0.44
4	0.1006		0.26
5	0.1001		0.75
6	0.1048		-3.91
7	0.0979		2.93
8	0.1017		-0.83
9	0.1005		0.36
10	0.0988		2.04

Line Chart4: Weight Variation of Salbutal



Discussion: Maximum percentage difference allowed for tablets with average weight 130mg or less is ±10. In this study average weight of Sultolin, Ventolin, Brodil and Salbutal was found 0.17103gm, 0.20097gm, 0.19688gm and 0.10086gm respectively.

Result: It is seen that, average weight of Sultolin, Ventolin, Brodil and Salbutal have met the limit (±10% of average wt.) permitted by the USP XX-NF XV.

Friability Study

Another measure of tablet's strength is its friability. Tablets that tend to powder, chip, and fragment when handled lack elegance and consumer acceptance, and can create excessively dirty process in such areas of manufacturing as coating and packaging. They can also add to tablet's weight variation or content uniformity problems. Conventional compressed tablets that lose less than 0.5 to 1% of their weight are generally considered acceptable. (Lachman, L., 1986)

Methodology: A friability test was performed with salbutamol tablets of four brands (Sultolin, Ventolin, Brodil and Salbutal) using the Roche friabilator. Ten tablets were taken from each brand for the test. All the tablets were weighed before placing in the friabilator. At first, ten tablets of one brand were placed in the friabilator and operated for 100 revolutions. Then all the tablets were dusted and reweighed. The same process was performed for the rest thirty salbutamol tablets of other three brands. The percent friability of the tablets was measured using the following formula:

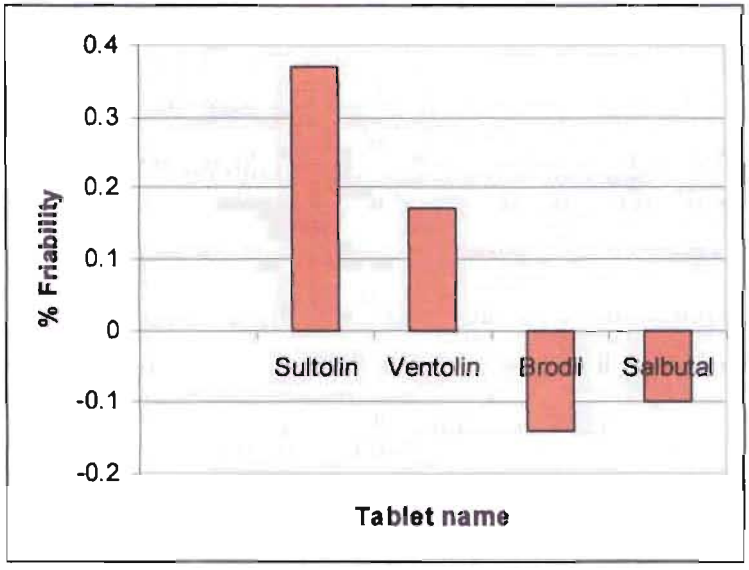
(1-Initial weight/Final weight) ×100

The measured values were recorded in the Table 9.

Table9: Percent(%) Friability of Sultolin, Ventolin, Brodil and Salbutal

Tablet Sample	Initial weight of 10 tablets	Final weight of 10 tablets	Percent(%) Friability
Sultolin	1.7103	1.7166	0.37
Ventolin	2.0097	2.0131	0.17
Brodil	1.9688	1.966	-0.14
Salbutal	1.0086	1.0076	-0.10

Bar Diagram1: Percent(%) Friability of Sultolin, Ventolin, Brodil and Salbutal



Discussion: The percent(%) friability of Sultolin, Ventolin, Brodil and Salbutal were 0.37, 0.17, -0.14 and -0.10 respectively. Tablets are acceptable if they lose less than 0.5 to 1% of their weight. Otherwise tablets will not be accepted for use.

Result: In this experiment it was found that, % friability of Sultolin, Ventolin, Brodil and Salbutal were within the acceptable range.

Hardness Study

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. In addition tablets should be able to withstand reasonable abuse when in the hands of the consumer. Adequate tablet hardness is necessary requisite for consumer acceptance. More recently, the relationship of hardness to tablet disintegration, and perhaps more significantly, to the drug dissolution release rate, has become apparent. The monitoring of tablet hardness is especially important for drug products that possess real or potential bioavailability problems or that are sensitive to altered dissolution release profiles as a function of the compressive force employed.

Historically, the strength of a tablet was determined by breaking it between the second and third fingers with the thumb acting as a fulcrum. If there was a sharp snap, the tablet was deemed to have acceptable strength. More recently, however, tablet hardness has been defined as the force required to break a tablet in a diametric compression test. To perform this test, a tablet is placed between two anvils, force is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded. Hardness is thus sometimes termed the *tablet crushing strength*. Several devices operating in this manner have been and continue to be used to test tablet hardness. These are Monsanto tester, the Strong-Cobb tester, the Pfizer tester, the Erweka tester, and the Schleuniger tester. (Lachman, L., 1986)

Methodology: The hardness test of salbutamol tablets of four brands (Sultolin, Ventolin, Brodil and Salbutal) was performed using the Monsanto hardness tester. Ten tablets from each brand were taken for the purpose of the test. Firstly, the lower plunger of the tester was placed in contact with the tablet and a zero reading was taken. The upper plunger was then forced against a spring until the tablet fractured. The force required to break the tablet was then recorded in Newton, and the zero reading was deducted from it. The same procedure was done to measure

the hardness of the rest thirty nine tablets. The readings of the forces were recorded in the Table 10, Table 11, Table12 and Table 13.

Table10: Hardness of Sultolin

	Sultolin	
Tab no.	Hardness (kg)	Hardness (N)
1	1.1	10.79
2	1.1	10.79
3	0.7	6.87
4	1.5	14.72
5	0.7	6.87
6	0.9	8.83
7	0.8	7.85
8	1.2	11.77
9	1.3	12.75
10	0.9	8.83

Bar Diagram 2: Hardness of Sultolin

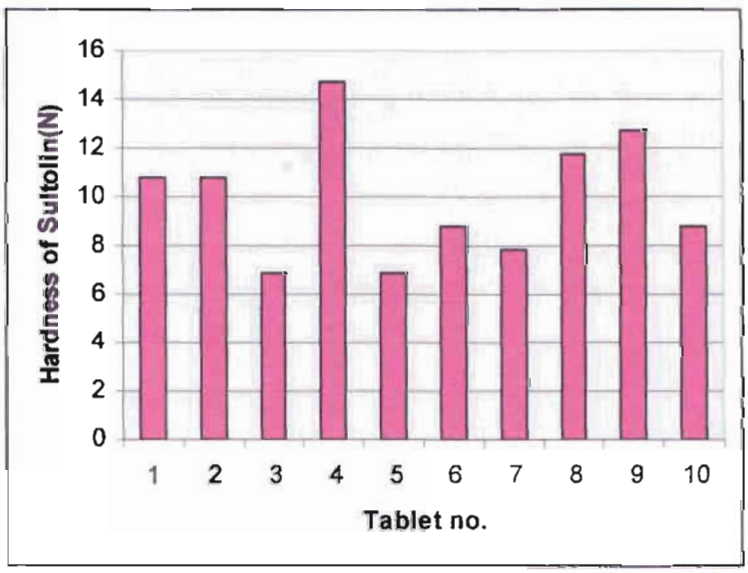


Table11: Hardness of Ventolin

	Ventolin	
Tab no.	**Hardness (kg)**	**Hardness (N)**
1	1	9.81
2	1.4	13.73
3	1.26	12.36
4	1.1	10.79
5	1.1	10.79
6	1.5	14.72
7	1.75	17.17
8	1.3	12.75
9	1.5	14.72
10	1.05	10.3

Bar Diagram3: Hardness of Ventolin

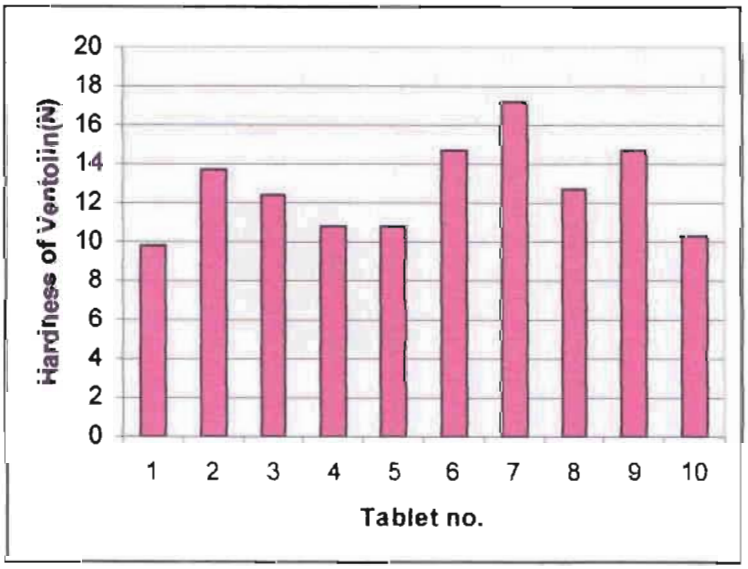


Table12: Hardness of Brodil

	Brodil	
Tab no.	Hardness (kg)	Hardness (N)
1	1.6	15.7
2	1.3	12.75
3	1.3	12.75
4	1.1	10.79
5	1.6	15.7
6	1.5	14.72
7	1.5	14.72
8	1.4	13.73
9	2	19.62
10	1.7	16.68

Bar Diagram4: Hardness of Brodil

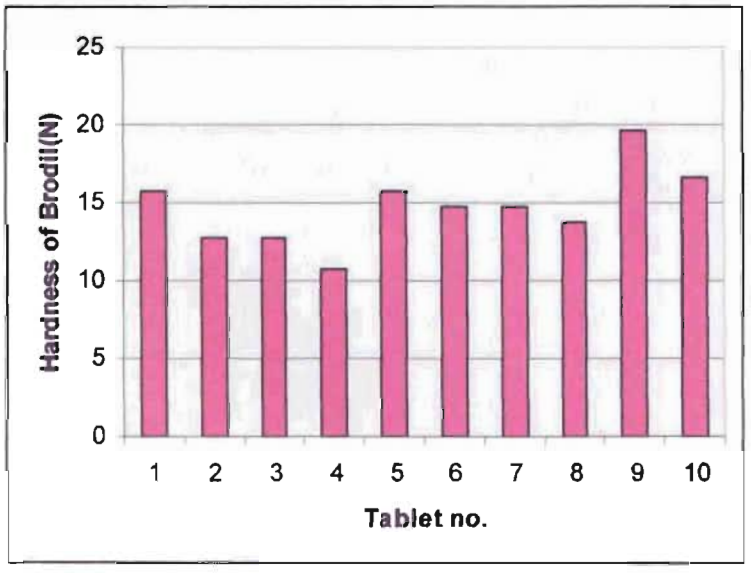
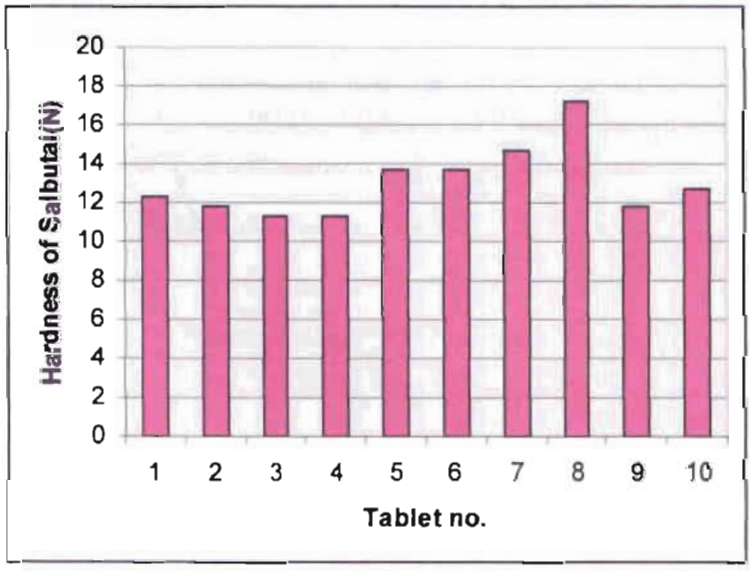


Table13: Hardness of Salbutal

	Salbutal	
Tab no.	Hardness (kg)	Hardness (N)
1	1.25	12.26
2	1.2	11.77
3	1.15	11.28
4	1.15	11.28
5	1.4	13.73
6	1.4	13.73
7	1.5	14.72
8	1.75	17.17
9	1.2	11.77
10	1.3	12.75

Bar Diagram5: Hardness of Salbutal



Discussion: The average crushing strength of Sultolin, Ventolin, Brodil and Salbutal were 10.007N, 11.64N, 14.72 N and 13.04N respectively. The lowest crushing strength and highest crushing strength for Sultolin were 6.87N and 14.72N respectively. The lowest crushing strength and highest crushing strength for Ventolin were 9.41N and

17.17N respectively. The lowest crushing strength and highest crushing strength of Brodil were 10.79N and 19.62 N respectively. The lowest crushing strength for and highest crushing strength for Salbutal were 11.28N and 17.17N respectively.

Result: From the above discussion it can be said that, the hardness value or crushing strength of Sultolin widely differ for individual tablet from the average. The highest hardness value of Ventolin differs a lot from average. The range of crushing strength of Brodil also differs a lot from the average value. The range of hardness value of Salbutal was almost close to the average value.

Dissolution Study

Dissolution tests and test specifications have now been developed for nearly all tablet products. The rate of drug absorption from acidic drug moieties that are absorbed high in GI tract is often determined by the rate of drug dissolution from the tablet. If the attainment of high peak blood levels for the drug is a product objective, obtaining rapid drug dissolution from the tablet is usually critically important. The rate of dissolution may thus be directly related to the efficacy of the tablet product, as well as to bioavailability differences between formulations. Therefore, an evaluation as to whether or not a tablet releases its drug contents when placed in the environment of the gastrointestinal tract is often of fundamental concern to the tablet formulator. The most direct assessment of a drug's release from various tablet formulations or products is accomplished through in vivo bioavailability measurements. The use of in vivo studies is restricted for several reasons; the length of time needed to plan, conduct and interpret the study; the highly skilled personnel required for human studies; the low precision and high variability typical of the measurements; the high cost of the studies; the use of human subjects for "nonessential" research; and the necessary assumption that a perfect correlation exists between diseased patients and the healthy human subjects used in the test. Consequently in vitro dissolution tests have been extensively studied, developed and used as an indirect

measurement of drug availability, especially in preliminary assessments of formulation factors and manufacturing methods that are likely to influence bioavailability. As with any in vitro test, it s critically important that the dissolution test be correlated with in vivo bioavailability tests. Two objectives in the development of in vitro dissolution tests are to show (1) that the release of the drug from the tablet is as close as possible to 100% and (2) that the rate of drug release is uniform batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective. (Lachman, L., 1986)

Dissolution Medium Preparation:

Methodology: A 10gm/L solution of Hydrochloric acid (HCl) was to be prepared as recommended in British Pharmacopoeia (BP). 32%w/v HCl was supplied by the East West University laboratory. In this solution 32 gm HCl is present in 100ml. So, 10gm HCl is present in 31.25ml solution. This 31.25ml HCl was withdrawn using a pipette and was replaced in a beaker. Then water was added to make the solution 1000ml. From this 1000ml solution again 10 ml of solution was withdrawn and was made up to 1000ml by diluting with 900ml water. This solution was used as the medium for dissolution according to the BP. It was also used as blank solution. To prepare the standard solution 0.008gm of crude salbutamol sulphate was weighed in an electronic balance. This crude sample was then dissolved in 100ml of dissolution medium of HCl prepared earlier. From this solution again 10 ml was taken and diluted with the dissolution medium by making the solution up to 100ml. Finally the concentration of the crude salbutamol sulphate solution was 0.008mg/ml. The solution was then taken in a test tube for measuring its absorbance.

Conducting the Dissolution Test

To investigate the in vitro release profile kinetics of the salbutamol tablets, dissolution test were performed using BP XII D Apparatus 1 (Basket apparatus) by dissolution tester (RC6, Vanguard Pharmaceuticals, USA). Four individual vessels were used for four individual brands. Each vessel was filled with 1000ml of dissolution medium of HCl

prepared earlier. The temperature of the dissolution test apparatus was set at 37° C (± 0.5 °C) and time was fixed up to 120 minutes. As soon as the temperature of the apparatus reached at 37°C two 4mg tablets from each brand were placed in four individual vessels. 10 ml of sample solution from each vessel were withdrawn at regular intervals of 10, 20, 30, 45, 60, 90 and 120 minutes. Each time the sample was withdrawn, lost amount was filled with the blank solution. All the sample solutions were placed in separate test tubes. The solutions withdrawn at different intervals were then ready for measuring absorbance.

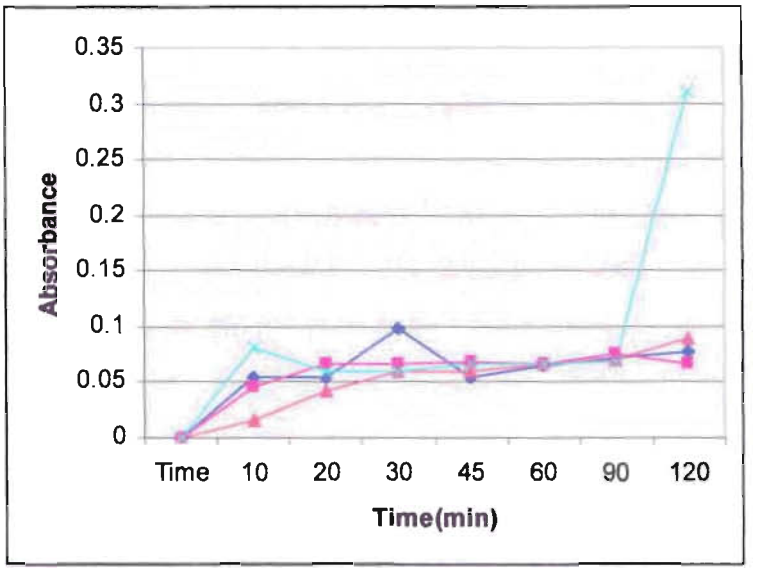
Determination of Absorbance

The absorbance of all the sample solutions and the standard solution of crude salbutamol sulphate were measured using single beam spectrophotometer (HACH, Model no DR/400UV-VIS, USA) at 276nm as directed by the BP. At first, the absorbance of the spectrophotometer was set to 0 reading using the blank solution. Then absorbance of the sample solutions taken at 10, 20, 30, 45, 60, 90 and 120 minutes were measured and recorded in the Table 14.

Table14: Absorbance of Sultolin, Ventolin, Brodil and Salbutal after Dissolution

	Absorbance of Tablets			
Time	**Sultolin**	**Ventolin**	**Brodil**	**Salbutal**
10	0.054	0.081	0.015	0.045
20	0.055	0.059	0.042	0.066
30	0.098	0.059	0.060	0.067
45	0.055	0.067	0.060	0.069
60	0.064	0.067	0.067	0.067
90	0.072	0.069	0.070	0.076
120	0.077	0.309	0.090	0.066

Line Chart5: Absorbance of Sultolin, Ventolin, Brodil and Salbutal after Dissolution



Absorbance of Standard Solution of Crude Salbutamol Sulphate

The absorbance of the standard solution of crude salbutamol sulphate was measured using single beam spectrophotometer (HACH, Model no DR/400UV-VIS, USA) at 276nm as directed by the BP. The absorbance value was found 0.035.

Discussion: In this study, the absorbance of the tablets is supposed to be increased with the time.

In case of Sultolin we see that, the absorbance of the tablet had increased initially with mild change but, after 30 minutes there was a sudden high increase in the absorbance (0.098). Then, the absorbance had decreased to 0.055and again increased with little change till the end (120min). This type of sudden variation in absorbance is not acceptable for a tablet.

In case of Ventolin it was seen that, initially absorbance had decreased in 20 minutes. Then, absorbance has increased gradually till 90 minutes. After 120 minutes there was a drastic increase in the absorbance (0.309) which is very unusual.

Absorbance values of Brodil had gradually increased with the time. There was no sudden unexpected change in case of Brodil.

In case of Salbutal, initially absorbance values increased gradually. The absorbance after 60 minutes and 120 minutes were 0.067 and 0.066 respectively. These two absorbance values had deviated from the normal phenomena.

The absorbance of standard solution of crude salbutamol sample was found 0.035.

Result: From the above discussion, the absorbance value of Sultolin after 30 minutes cannot be accepted for explaining the release profile of the tablet. For Ventolin absorbance after 10 minutes and 120 minutes are not acceptable. In case of Brodil the absorbance pattern with time was quite satisfactory. For Salbutal, the absorbance value after 60minutes and 120 minutes are not acceptable for interpreting the release profile kinetics of the tablet. Among the sample salbutamol tablets no tablet met the standard absorbance value.

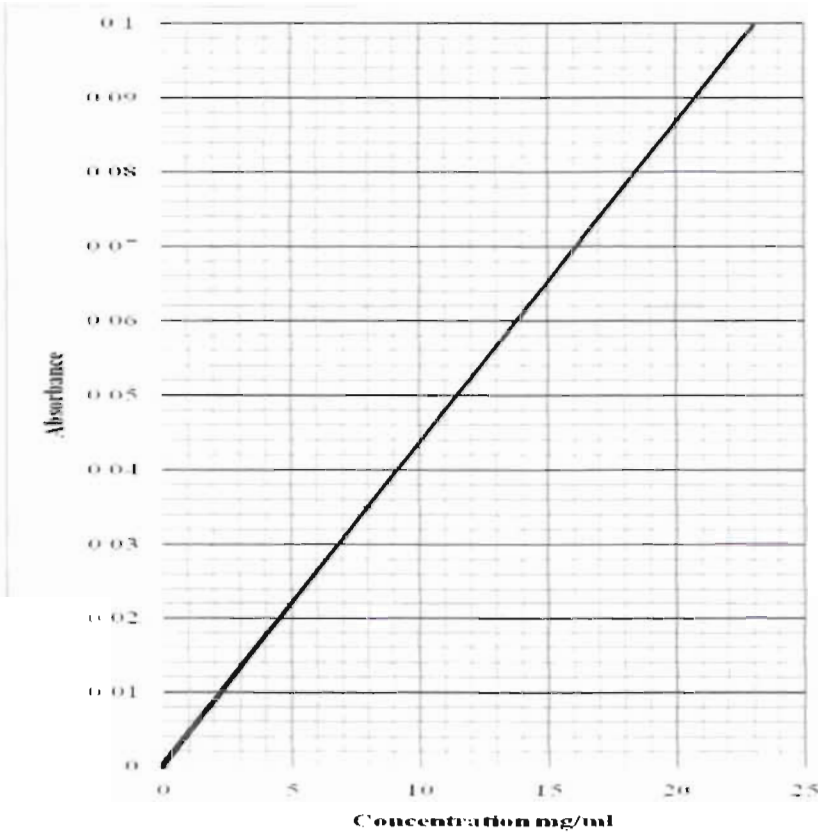
Standard Curve Preparation

To determine the concentrations of the salbutamol solution of four brands at different time interval, it was necessary to prepare a standard curve. For this purpose, at first 0.008gm of crude salbutamol sulphate was weighed in an electronic balance. This crude sample was then dissolved in 100ml of dissolution medium of HCl prepared earlier. From this solution again 10 ml was taken and diluted with the dissolution medium by making the solution up to 100ml. Finally the concentration of the crude salbutamol sulphate solution was 0.008mg/ml. The solution was then taken in a test tube for measuring its absorbance. The absorbance of this standard solution of crude salbutamol sulphate was measured using single beam spectrophotometer (HACH, Model no DR/400UV-VIS,

USA) at 276nm as directed by the BP. The absorbance value was found 0.035. A line chart (Line Chart6) was prepared by plotting the absorbance value against the concentration in Microsoft Excel 2003.

Each box in X axis was assumed to be equal to 1 unit and each 5 box of Y axis was assumed to be equal to 0.01unit.

Line Chart6: Standard Curve of Crude Salbutamol Sulphate at 276nm



Determination of Concentrations of Sultolin, Ventolin, Brodil and Salbutal Using the Standard Curve:

Concentrations of Sultolin, Ventolin, Brodil and Salbutal after 10, 20, 30, 45, 60, 90 and 120 minutes were determined using the standard curve of crude salbutamol sulphate. The absorbances of the different salbutamols were plotted in the Y-axis. From each absorbance point of Y-axis a horizontal line was drawn which intersected on a point of the standard curve. From each intersected point on standard curve a line was drawn

perpendicularly toward the X-axis. Each line intersected at different points on X-axis representing the concentrations of different brand of salbutamol at different time intervals. The determined concentrations were recorded in Table 15.

Table15: Concentration of Sultolin, Ventolin, Brodil and Salbutal determined from Standard Curve

	Concentration (mg/ml)			
Time	**Sultolin**	**Ventolin**	**Brodil**	**Salbutal**
10	12.2	18.2	3.2	10.1
20	12.5	13.2	9.4	15
30	22.7	13.2	13.7	15.1
45	12.5	15.1	13.7	15.6
60	14.4	15.1	15.1	15.1
90	16.2	15.6	15.9	17.1
120	17.2	-	20.9	15

Discussion: The concentrations of Sultolin, Ventolin, Brodil and Salbutal increased with time which is required for proper release and subsequent action of the tablet. Only a few points showed deviation from the continuous increase pattern. For Sultolin 30 minute was not acceptable. In case of Ventolin concentration after 10 and 120 minutes cannot be accepted. Brodil showed comparatively satisfactory pattern of drug release with time. In case of Salbutal 60 minute and 120 minute gave unusual result.

Limitations:

During completion of our research work a number of problems aroused despite of which we had to carry on our research experiments the limitations which we had to face are as follows:

- The most unusual limitation was the unavailability of distilled water. For this reason we had to execute our experiments with tap water.
- Secondly, the Monsanto Hardness tester was not performing perfectly all the time for which, there were mark able variations in crushing strength among the tablets.
- Next, I want to mention about the dissolution tester which did not function appropriately. It was a major limitation of our research.
- The sample solutions should have been filtered properly after withdrawing from the vessel of the dissolution tester but we did not attempt to do that.

Another limitation was that, we could not maintain the environment moisture free which was acutely required as salbutamol is very much hygroscopic.

Recommendations:

In this research work no proper linear relationship was found between the release profile and the drugs. May be the result would have been perfect if following recommendations were available:

- Distilled water
- Proper functioning hardness tester
- Proper functioning dissolution tester
- Filtration of the sample solutions after withdrawing from the dissolution tester vessel

Conclusion:

In conclusion, it can be mentioned that, for several limitations the research work was not up to the mark. No single brand met all the requirements properly. In case of hardness only Salbutal tablets were close to the average weight. There were huge variations in hardness values among the tablets of Ventolin, Brodil and Sultolin. Thickness values were same for all the tablets within individual brand. The absorbance values were not closer to the standard value of crude salbutamol sulphate. Sultolin and Brodil had good absorbance values than Ventolin and Salbutal. The release profile kinetics was not uniform in any of the brands.

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